

Claims

What is claimed is:

1. A cell adhesion modulating agent that:
 - (a) comprises a claudin CAR sequence; and
 - (b) contains 3-16 amino acid residues linked by peptide bonds.

- ✓ 2. *B1* A modulating agent that:
(a) comprises at least five consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

- (b) contains no more than 50 consecutive amino acid residues present within the claudin.

- ✓ 3. A modulating agent that:
(a) comprises at least seven consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

4. A modulating agent that:

(a) comprises at least eight consecutive amino acid residues of a claudin CAR sequence having the formula:

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine; and

(b) contains no more than 50 consecutive amino acid residues present within the claudin.

5. A modulating agent according to any one of claims 2-4, wherein the agent is a peptide ranging in size from 3 to 50 amino acid residues.

6. A modulating agent according to any one of claims 1-4, wherein the agent is a peptide ranging in size from 4 to 16 amino acid residues.

7. A modulating agent according to any one of claims 1-4, wherein the CAR sequence is present within a cyclic peptide.

8. A modulating agent according to claim 7, wherein the cyclic peptide has the formula:

(Z₁)-(Y₁)-(X₁)-(W)-(X₂)-(Y₂)-(Z₂);
[]

wherein W is a tetrapeptide selected from the group consisting of IYSY (SEQ ID NO:2), TSSY (SEQ ID NO:3), VTAF (SEQ ID NO:4), and VSAF (SEQ ID NO:5);

wherein X_1 , and X_2 are optional, and if present, are independently selected from the group consisting of amino acid residues and combinations thereof in which the residues are linked by peptide bonds, and wherein X_1 and X_2 independently range in size from 0 to 10 residues, such that the sum of residues contained within X_1 and X_2 ranges from 1 to 12;

wherein Y_1 and Y_2 are independently selected from the group consisting of amino acid residues, and wherein a covalent bond is formed between residues Y_1 and Y_2 ; and

wherein Z_1 and Z_2 are optional, and if present, are independently selected from the group consisting of amino acid residues and combinations thereof in which the residues are linked by peptide bonds.

9. A modulating agent according to claim 8, wherein Z_1 is not present and Y_1 comprises an N-acetyl group.

10. A modulating agent according to claim 8, wherein Z_2 is not present and Y_2 comprises a C-terminal amide group.

11. A modulating agent according to claim 8, wherein Y_1 and Y_2 are covalently linked via a disulfide bond.

12. A modulating agent according to claim 11, wherein Y_1 and Y_2 are each independently selected from the group consisting of penicillamine, β,β -tetramethylene cysteine, β,β -pentamethylene cysteine, β -mercaptopropionic acid, β,β -pentamethylene- β -mercaptopropionic acid, 2-mercaptobenzene, 2-mercaptoaniline, 2-mercaptoproline and derivatives thereof.

13. A modulating agent according to claim 11, wherein Y_1 and Y_2 are cysteine residues or derivatives thereof.

14. A modulating agent according to claim 8, wherein Y₁ and Y₂ are covalently linked via an amide bond.

15. A modulating agent according to claim 14, wherein the amide bond is formed between terminal functional groups.

16. A modulating agent according to claim 14, wherein the amide bond is formed between residue side-chains.

17. A modulating agent according to claim 14, wherein the amide bond is formed between one terminal functional group and one residue side chain.

18. A modulating agent according to claim 14, wherein:

(a) Y₁ is selected from the group consisting of lysine, ornithine, and derivatives thereof and Y₂ is selected from the group consisting of aspartate; glutamate and derivatives thereof; or

(b) Y₂ is selected from the group consisting of lysine, ornithine and derivatives thereof and Y₁ is selected from the group consisting of aspartate, glutamate and derivatives thereof.

19. A modulating agent according to claim 8, wherein Y₁ and Y₂ are covalently linked via a thioether bond.

20. A modulating agent according to claim 8, wherein Y₁ and Y₂ are each tryptophan or a derivative thereof, such that the covalent bond generates a δ₁δ₁-ditryptophan, or a derivative thereof.

21. A polynucleotide encoding a modulating agent according to any one of claims 1-4.

22. An expression vector comprising a polynucleotide according to claim 21.

23. A host cell transformed or transfected with an expression vector according to claim 22.

24. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to a claudin CAR sequence and modulates a claudin-mediated function, wherein the claudin CAR sequence has the formula:

Trp-Lys/Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine.

25. A modulating agent comprising a mimetic of a claudin CAR sequence that comprises at least three consecutive amino acid residues of a claudin CAR sequence having the formula

Trp-Lys/Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine;

wherein the mimetic is capable of modulating a claudin-mediated function.

26. A modulating agent comprising a mimetic of a claudin CAR sequence that comprises at least five consecutive amino acid residues of a claudin CAR sequence having the formula

Trp-Lys/Arg-Aaa-Baa-Ser/Ala-Tyr/Phe-Caa-Gly (SEQ ID NO:1)

wherein Aaa, Baa and Caa indicate independently selected amino acid residues; Lys/Arg is an amino acid that is lysine or arginine; Ser/Ala is an amino acid that is serine or alanine; and Tyr/Phe is an amino acid that is tyrosine or phenylalanine;
wherein the mimetic is capable of modulating a claudin-mediated function.

27. A modulating agent according to any one of claims 1-4 or 24-26 linked to a drug.

28. A modulating agent according to any one of claims 1-4 or 24-26 linked to a detectable marker.

29. A modulating agent according to any one of claims 1-4 or 24-26 linked to a targeting agent.

30. A modulating agent according to any one of claims 1-4 or 24-26 linked to a support material.

31. A modulating agent according to claim 30, wherein the support material is a polymeric matrix.

32. A modulating agent according to claim 30, wherein the support material is selected from the group consisting of plastic dishes, plastic tubes, sutures, membranes, ultra thin films, bioreactors and microparticles.

33. A cell adhesion modulating agent according to any one of claims 1-4 or 24-26, further comprising one or more of:

(a) a cell adhesion recognition sequence that is bound by an adhesion molecule other than a claudin, wherein the cell adhesion recognition sequence is separated from any claudin CAR sequence(s) by a linker; and/or

Part B 3 cont'd

(b) an antibody or antigen-binding fragment thereof that specifically binds to a cell adhesion recognition sequence bound by an adhesion molecule other than a claudin.

34. A cell adhesion modulating agent according to claim 33, wherein the adhesion molecule is selected from the group consisting of integrins, cadherins, occludin, N-CAM, fibronectin, laminin, and other extracellular matrix proteins.

Part B 4

35. A pharmaceutical composition comprising a cell adhesion modulating agent according to any one of claims 1-4 or 24-26, in combination with a pharmaceutically acceptable carrier.

36. A composition according to claim 35, further comprising a drug.

37. A composition according to claim 35, wherein the cell adhesion modulating agent is present within a sustained-release formulation.

38. A composition according to claim 35, further comprising one or more of:

(a) a peptide comprising a cell adhesion recognition sequence that is bound by an adhesion molecule other than a claudin; and/or
(b) an antibody or antigen-binding fragment thereof that specifically binds to a cell adhesion recognition sequence bound by an adhesion molecule other than a claudin.

39. A composition according to claim 38, wherein the adhesion molecule is selected from the group consisting of integrins, cadherins, occludin, N-CAM, fibronectin, laminin and other extracellular matrix proteins.

40. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more claudin-1 CAR sequences selected from the group consisting of: IYSY (SEQ ID NO:2), IYSYA (SEQ ID NO:27), IYSYAG (SEQ ID NO:28), KIYSY (SEQ

*Part B
Claim*

ID NO:29), KIYSYA (SEQ ID NO:30), KIYSYAG (SEQ ID NO:31), WKIYSY (SEQ ID NO:32), WKIYSYA (SEQ ID NO:33) and WKIYSYAG (SEQ ID NO:34).

41. A modulating agent according to claim 40, wherein the agent comprises a linear peptide having the sequence N-Ac-WKIYSYAG-NH₂ (SEQ ID NO:34).

42. A modulating agent according to claim 40, wherein a claudin-1 CAR sequence is present within a cyclic peptide.

43. A modulating agent according to claim 42, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CIYSYC (SEQ ID NO:59), CIYSYAC (SEQ ID NO:60), CIYSYAGC (SEQ ID NO:61), CKIYSYC (SEQ ID NO:62), CKIYSYAC (SEQ ID NO:63), CKIYSYAGC (SEQ ID NO:64), CWKIYSYC (SEQ ID NO:65), CWKIYSYAC (SEQ ID NO:66), CWKIYSYAGC (SEQ ID NO:67), KIYSYD (SEQ ID NO:68), KIYSYAD (SEQ ID NO:69), KIYSYAGD (SEQ ID NO:70), KKIYSYD (SEQ ID NO:71), KKIYSYAD (SEQ ID NO:72), KKIYSYAGD (SEQ ID NO:73), KWKIYSYD (SEQ ID NO:74), KWKIYSYAD (SEQ ID NO:75), KWKIYSYAGD (SEQ ID NO:76), KIYSYE (SEQ ID NO:77), KIYSYAE (SEQ ID NO:78), KIYSYAGE (SEQ ID NO:79), KKIYSYE (SEQ ID NO:80), KKIYSYAE (SEQ ID NO:81), KKIYSYAGE (SEQ ID NO:82), KWKIYSYE (SEQ ID NO:83), KWKIYSYAE (SEQ ID NO:84), KWKIYSYAGE (SEQ ID NO:85), DIYSYK (SEQ ID NO:86), DIYSYAK (SEQ ID NO:87), DIYSYAGK (SEQ ID NO:88), DKIYSYK (SEQ ID NO:89), DKIYSYAK (SEQ ID NO:90), DKIYSYAGK (SEQ ID NO:91), DWKIYSYK (SEQ ID NO:92), DWKIYSYAK (SEQ ID NO:93), DWKIYSYAGK (SEQ ID NO:94), EIYSYK (SEQ ID NO:95), EIYSYAK (SEQ ID NO:96), EIYSYAGK (SEQ ID NO:97), EKIYSYK (SEQ ID NO:98), EKIYSYAK (SEQ ID NO:99), EKIYSYAGK (SEQ ID NO:100), EWKIYSYK (SEQ ID NO:101), EWKIYSYAK (SEQ ID NO:102), EWKIYSYAGK (SEQ ID NO:103), IYSYA (SEQ ID NO:104), IYSYAG (SEQ ID NO:105), KIYSY (SEQ ID NO:106), KIYSYAG (SEQ ID NO:107), WKIYSY (SEQ ID NO:108), WKIYSYA (SEQ ID NO:109) and WKIYSYAG (SEQ ID NO:110).

44. A polynucleotide encoding a modulating agent according to claim 40.

45. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the claudin-1 CAR sequence WKIYSYAG (SEQ ID NO:34).

46. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more claudin-2 CAR sequences selected from the group consisting of: TSSY (SEQ ID NO:3), TSSYV (SEQ ID NO:35), TSSYVG (SEQ ID NO:36), RTSSY (SEQ ID NO:37), RTSSYV (SEQ ID NO:38), RTSSYVG (SEQ ID NO:39), WRTSSY (SEQ ID NO:40), WRTSSYV (SEQ ID NO:41) and WRTSSYVG (SEQ ID NO:42).

47. A modulating agent according to claim 46, wherein the agent comprises a linear peptide having the sequence N-Ac-WRTSSYVG-NH₂ (SEQ ID NO:42).

48. A modulating agent according to claim 46, wherein a claudin-2 CAR sequence is present within a cyclic peptide.

49. A modulating agent according to claim 48, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CTSSYC (SEQ ID NO:111), CTSSYVC (SEQ ID NO:112), CTSSYVGC (SEQ ID NO:113), CRTSSYC (SEQ ID NO:114), CRTSSYVC (SEQ ID NO:115), CRTSSYVGC (SEQ ID NO:116), CWRTSSYC (SEQ ID NO:117), CWRTSSYVC (SEQ ID NO:118), CWRTSSYVGC (SEQ ID NO:119), KTSSYD (SEQ ID NO:120), KTSSYVD (SEQ ID NO:121), KTSSYVGD (SEQ ID NO:122), KRTSSYD (SEQ ID NO:123), KRTSSYVD (SEQ ID NO:124), KRTSSYVGD (SEQ ID NO:125), KWRTSSYD (SEQ ID NO:126), KWRTSSYVD (SEQ ID NO:127), KWRTSSYVGD (SEQ ID NO:128), KTSSYE (SEQ ID NO:129), KTSSYVE (SEQ ID NO:130), KTSSYVGE (SEQ ID NO:131), KRTSSYE (SEQ ID NO:132), KRTSSYVE (SEQ ID NO:133), KRTSSYVGE (SEQ ID NO:134), KWRTSSYE (SEQ ID NO:135), KWRTSSYVE (SEQ ID NO:136), KWRTSSYVGE (SEQ ID NO:137), DTSSYK (SEQ ID

NO:138), DTSSYVK (SEQ ID NO:139), DTSSYVGK (SEQ ID NO:140), DRTSSYK (SEQ ID NO:141), DRTSSYVK (SEQ ID NO:142), DRTSSYVGK (SEQ ID NO:143), DWRTSSYK (SEQ ID NO:144), DWRTSSYVK (SEQ ID NO:145), DWRTSSYVGK (SEQ ID NO:146), ETSSYK (SEQ ID NO:147), ETSSYVK (SEQ ID NO:148), ETSSYVGK (SEQ ID NO:149), ERTSSYK (SEQ ID NO:150), ERTSSYVK (SEQ ID NO:151), ERTSSYVGK (SEQ ID NO:152), EWRTSSYK (SEQ ID NO:153), EWRTSSYVK (SEQ ID NO:154), EWRTSSYVGK (SEQ ID NO:155), TSSYV (SEQ ID NO:156), TSSYVG (SEQ ID NO:157), RTSSY (SEQ ID NO:158), RTSSYV (SEQ ID NO:159), RTSSYVG (SEQ ID NO:160), WRTSSY (SEQ ID NO:161), WRTSSYV (SEQ ID NO:162) and WRTSSYVG (SEQ ID NO:163).

50. A polynucleotide encoding a modulating agent according to claim 46.

51. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the claudin-2 CAR sequence WRTSSYVG (SEQ ID NO:42).

52. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more CPE-R CAR sequences selected from the group consisting of: VTAF (SEQ ID NO:4), VTAFI (SEQ ID NO:43), VTAFIG (SEQ ID NO:44), RVTAF (SEQ ID NO:45), RVTAFI (SEQ ID NO:46), RVTAFIG (SEQ ID NO:47), WRVTAF (SEQ ID NO:48), WRVTAFI (SEQ ID NO:49) and WRVTAFIG (SEQ ID NO:50).

53. A modulating agent according to claim 52, wherein the agent comprises a linear peptide having the sequence N-Ac-WRVTAFIG-NH₂ (SEQ ID NO:50).

54. A modulating agent according to claim 52, wherein a CPE-R CAR sequence is present within a cyclic peptide.

55. A modulating agent according to claim 54, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CVT AFC (SEQ ID NO:164), CVT AFIC (SEQ ID NO:165), CVT AFIGC (SEQ ID NO:166), CRV T AFC (SEQ ID NO:167), CRV TAF IC (SEQ ID NO:168), CRV TAF IGC (SEQ ID NO:169), CWR VTA FC (SEQ ID NO:170), CWR VTAF IC (SEQ ID NO:171), CWR VTAFIG C (SEQ ID NO:172), KVT AFD (SEQ ID NO:173), KVT AFID (SEQ ID NO:174), KVT AFIGD (SEQ ID NO:175), KRV TAFD (SEQ ID NO:176), KRV TAFIGD (SEQ ID NO:177), KRV TAFID (SEQ ID NO:178), KWR VTAFD (SEQ ID NO:179), KWR VTAFID (SEQ ID NO:180), KWR VTAFIGD (SEQ ID NO:181), KVT AFE (SEQ ID NO:182), KVT AFIE (SEQ ID NO:183), KVT AFIGE (SEQ ID NO:184), KRV TAFE (SEQ ID NO:185), KRV TAFIE (SEQ ID NO:186), KRV TAFIGE (SEQ ID NO:187), KWR VTAFE (SEQ ID NO:188), KWR VTAFIE (SEQ ID NO:189), KWR VTAFIGE (SEQ ID NO:190), DVAT FK (SEQ ID NO:191), DVT AFK (SEQ ID NO:192), DVT AFIGK (SEQ ID NO:193), DRV TAFK (SEQ ID NO:194), DRV TAFIK (SEQ ID NO:195), DRV TAFIGK (SEQ ID NO:196), DWR VTAFK (SEQ ID NO:197), DWR VTAFK (SEQ ID NO:198), DWR VTAFIGK (SEQ ID NO:199), EVT AFK (SEQ ID NO:200), EVT AFIK (SEQ ID NO:201), EVT AFIGK (SEQ ID NO:202), ERV TAFK (SEQ ID NO:203), ERV TAFIK (SEQ ID NO:204), ERV TAFIGK (SEQ ID NO:205), EWR VTAFK (SEQ ID NO:206), EWR VTAFIK (SEQ ID NO:207), EWR VTAFIGK (SEQ ID NO:208), VTA FI (SEQ ID NO:209), VTA FIG (SEQ ID NO:210), RVT AF (SEQ ID NO:211), RVT AFI (SEQ ID NO:212), RVT AFIG (SEQ ID NO:213), WRV TAF (SEQ ID NO:214), WRV TAFI (SEQ ID NO:215) and WRV TAFIG (SEQ ID NO:216).

56. A polynucleotide encoding a modulating agent according to claim 52.

57. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the CPE-R^{cav}CAR sequence WRVTAFIG (SEQ ID NO:50).

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58. A modulating agent according to any one of claims 1-4, wherein the agent comprises one or more RVP-1 CAR sequences selected from the group consisting of: VSAF (SEQ ID NO:5), VSAFI (SEQ ID NO:51), VSAFIG (SEQ ID NO:52), RVSAF (SEQ ID NO:53), RVSAFI (SEQ ID NO:54), RVSAFIG (SEQ ID NO:55), WRVSAF (SEQ ID NO:56), WRVSAFI (SEQ ID NO:57) and WRVSAFIG (SEQ ID NO:58).

59. A modulating agent according to claim 58, wherein the agent comprises a linear peptide having the sequence N-Ac-WRVSAFIG-NH₂ (SEQ ID NO:58). *Ref 203*

60. A modulating agent according to claim 58, wherein a RVP-1 CAR sequence is present within a cyclic peptide. *Ref 203*

61. A modulating agent according to claim 60, wherein the cyclic peptide comprises a sequence selected from the group consisting of: CVSAFC (SEQ ID NO:217), CVSAFIC (SEQ ID NO:218), CVSAFIGC (SEQ ID NO:219), CRVSAFC (SEQ ID NO:220), CRVSAFIC (SEQ ID NO:221), CRVSAFIGC (SEQ ID NO:222), CWRVSAFC (SEQ ID NO:223), CWRVSAFIC (SEQ ID NO:224), CWRVSAFIGC (SEQ ID NO:225), KVSAFD (SEQ ID NO:226), KVSAFID (SEQ ID NO:227), KVSAFIGD (SEQ ID NO:228), KRVSAFD (SEQ ID NO:229), KRVSAFID (SEQ ID NO:230), KRVSAFIGD (SEQ ID NO:231), KWRVSAFD (SEQ ID NO:232), KWRVSAFID (SEQ ID NO:233), KWRVSAFIGD (SEQ ID NO:234), KVSAFE (SEQ ID NO:235), KVSAFIE (SEQ ID NO:236), KVSAFIGE (SEQ ID NO:237), KRVSAFE (SEQ ID NO:238), KRVSAFIE (SEQ ID NO:239), KRVSAFIGE (SEQ ID NO:240), KWRVSAFE (SEQ ID NO:241), KWRVSAFIE (SEQ ID NO:242), KWRVSAFIGE (SEQ ID NO:243), DVSAFK (SEQ ID NO:244), DVSAFIK (SEQ ID NO:245), DVSAFIGK (SEQ ID NO:246), DRVSAFK (SEQ ID NO:247), DRVSAFIK (SEQ ID NO:248), DRVSAFIGK (SEQ ID NO:249), DWRVSAFK (SEQ ID NO:250), DWRVSAFIK (SEQ ID NO:251), DWRVSAFIGK (SEQ ID NO:252), EVSAFK (SEQ ID NO:253), EVSAFIK (SEQ ID NO:254), EVSAFIGK (SEQ ID NO:255), ERVSAFK (SEQ ID NO:256), ERVSFIGK (SEQ ID NO:257), ERVSAFIGK (SEQ ID NO:258), EWRVSAFK (SEQ ID NO:259), EWRVSAFIK (SEQ ID NO:260),

002 004 005 006 007 008 009 010 011 012 013 014 015 016 017 018 019 020 021 022 023 024 025 026 027 028 029 030 031 032 033 034 035 036 037 038 039 040 041 042 043 044 045 046 047 048 049 050 051 052 053 054 055 056 057 058 059 060 061 062 063 064 065 066 067 068 069 070 071 072 073 074 075 076 077 078 079 080 081 082 083 084 085 086 087 088 089 090 091 092 093 094 095 096 097 098 099 0100 0101 0102 0103 0104 0105 0106 0107 0108 0109 0110 0111 0112 0113 0114 0115 0116 0117 0118 0119 0120 0121 0122 0123 0124 0125 0126 0127 0128 0129 0130 0131 0132 0133 0134 0135 0136 0137 0138 0139 0140 0141 0142 0143 0144 0145 0146 0147 0148 0149 0150 0151 0152 0153 0154 0155 0156 0157 0158 0159 0160 0161 0162 0163 0164 0165 0166 0167 0168 0169 0170 0171 0172 0173 0174 0175 0176 0177 0178 0179 0180 0181 0182 0183 0184 0185 0186 0187 0188 0189 0190 0191 0192 0193 0194 0195 0196 0197 0198 0199 0200 0201 0202 0203 0204 0205 0206 0207 0208 0209 0210 0211 0212 0213 0214 0215 0216 0217 0218 0219 0220 0221 0222 0223 0224 0225 0226 0227 0228 0229 0230 0231 0232 0233 0234 0235 0236 0237 0238 0239 0240 0241 0242 0243 0244 0245 0246 0247 0248 0249 0250 0251 0252 0253 0254 0255 0256 0257 0258 0259 0260 0261 0262 0263 0264 0265 0266 0267 0268 0269 0270 0271 0272 0273 0274 0275 0276 0277 0278 0279 0280 0281 0282 0283 0284 0285 0286 0287 0288 0289 0290 0291 0292 0293 0294 0295 0296 0297 0298 0299 0300 0301 0302 0303 0304 0305 0306 0307 0308 0309 0310 0311 0312 0313 0314 0315 0316 0317 0318 0319 0320 0321 0322 0323 0324 0325 0326 0327 0328 0329 0330 0331 0332 0333 0334 0335 0336 0337 0338 0339 0340 0341 0342 0343 0344 0345 0346 0347 0348 0349 0350 0351 0352 0353 0354 0355 0356 0357 0358 0359 0360 0361 0362 0363 0364 0365 0366 0367 0368 0369 0370 0371 0372 0373 0374 0375 0376 0377 0378 0379 0380 0381 0382 0383 0384 0385 0386 0387 0388 0389 0390 0391 0392 0393 0394 0395 0396 0397 0398 0399 0400 0401 0402 0403 0404 0405 0406 0407 0408 0409 0410 0411 0412 0413 0414 0415 0416 0417 0418 0419 0420 0421 0422 0423 0424 0425 0426 0427 0428 0429 0430 0431 0432 0433 0434 0435 0436 0437 0438 0439 0440 0441 0442 0443 0444 0445 0446 0447 0448 0449 0450 0451 0452 0453 0454 0455 0456 0457 0458 0459 0460 0461 0462 0463 0464 0465 0466 0467 0468 0469 0470 0471 0472 0473 0474 0475 0476 0477 0478 0479 0480 0481 0482 0483 0484 0485 0486 0487 0488 0489 0490 0491 0492 0493 0494 0495 0496 0497 0498 0499 0500 0501 0502 0503 0504 0505 0506 0507 0508 0509 0510 0511 0512 0513 0514 0515 0516 0517 0518 0519 0520 0521 0522 0523 0524 0525 0526 0527 0528 0529 0530 0531 0532 0533 0534 0535 0536 0537 0538 0539 05310 05311 05312 05313 05314 05315 05316 05317 05318 05319 05320 05321 05322 05323 05324 05325 05326 05327 05328 05329 05330 05331 05332 05333 05334 05335 05336 05337 05338 05339 053310 053311 053312 053313 053314 053315 053316 053317 053318 053319 053320 053321 053322 053323 053324 053325 053326 053327 053328 053329 053330 053331 053332 053333 053334 053335 053336 053337 053338 053339 053340 053341 053342 053343 053344 053345 053346 053347 053348 053349 053350 053351 053352 053353 053354 053355 053356 053357 053358 053359 053360 053361 053362 053363 053364 053365 053366 053367 053368 053369 053370 053371 053372 053373 053374 053375 053376 053377 053378 053379 053380 053381 053382 053383 053384 053385 053386 053387 053388 053389 053390 053391 053392 053393 053394 053395 053396 053397 053398 053399 0533100 0533101 0533102 0533103 0533104 0533105 0533106 0533107 0533108 0533109 0533110 0533111 0533112 0533113 0533114 0533115 0533116 0533117 0533118 0533119 0533120 0533121 0533122 0533123 0533124 0533125 0533126 0533127 0533128 0533129 0533130 0533131 0533132 0533133 0533134 0533135 0533136 0533137 0533138 0533139 0533140 0533141 0533142 0533143 0533144 0533145 0533146 0533147 0533148 0533149 0533150 0533151 0533152 0533153 0533154 0533155 0533156 0533157 0533158 0533159 0533160 0533161 0533162 0533163 0533164 0533165 0533166 0533167 0533168 0533169 0533170 0533171 0533172 0533173 0533174 0533175 0533176 0533177 0533178 0533179 0533180 0533181 0533182 0533183 0533184 0533185 0533186 0533187 0533188 0533189 0533190 0533191 0533192 0533193 0533194 0533195 0533196 0533197 0533198 0533199 0533200 0533201 0533202 0533203 0533204 0533205 0533206 0533207 0533208 0533209 0533210 0533211 0533212 0533213 0533214 0533215 0533216 0533217 0533218 0533219 0533220 0533221 0533222 0533223 0533224 0533225 0533226 0533227 0533228 0533229 0533230 0533231 0533232 0533233 0533234 0533235 0533236 0533237 0533238 0533239 0533240 0533241 0533242 0533243 0533244 0533245 0533246 0533247 0533248 0533249 0533250 0533251 0533252 0533253 0533254 0533255 0533256 0533257 0533258 0533259 0533260 0533261 0533262 0533263 0533264 0533265 0533266 0533267 0533268 0533269 0533270 0533271 0533272 0533273 0533274 0533275 0533276 0533277 0533278 0533279 0533280 0533281 0533282 0533283 0533284 0533285 0533286 0533287 0533288 0533289 0533290 0533291 0533292 0533293 0533294 0533295 0533296 0533297 0533298 0533299 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053375150 053375151 053375152 053375153 053375154 053375155 053375156 0

EWRVSAFIGK (SEQ ID NO:261), VSAFI (SEQ ID NO:262), VSAFIG (SEQ ID NO:263), RVSAF (SEQ ID NO:264), RVSAFI (SEQ ID NO:265), RVSAFIG (SEQ ID NO:266), WRVSAF (SEQ ID NO:267), WRVSAFI (SEQ ID NO:268) and WRVSAFIG (SEQ ID NO:269).

62. A polynucleotide encoding a modulating agent according to claim 58.

63. A modulating agent comprising an antibody or antigen-binding fragment thereof that specifically binds to the RVP-1 CAR sequence WRVSAFIG (SEQ ID NO:58).
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